

Original Article

Preclusion of pain on injection with propofol: Evaluating the effects of lignocaine or fentanyl pretreatment

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Abstract

Background: Propofol (2,6-di-isopropylphenol) used for the induction of anesthesia often causes mild to severe pain or discomfort on injection, for which various methods have been tried, but with conflicting results.

Objective: The present study involved pretreatment with lignocaine, fentanyl and placebo for prevention of pain on propofol injection to determine the difference in efficacy of fentanyl 100 µg compared with lignocaine 40 mg.

Materials and Methods: Sixty-three participants of either sex, between 18 and 60 years of age, belonging to ASA physical status I and 2, undergoing elective surgery under general anesthesia, were randomized into three equal groups of 21 participants. They received, intravenously, either lignocaine (20 mg/mL) or fentanyl (50 µg/mL) or placebo (normal saline 2 mL) pretreatment before the propofol injection.

Results: The three groups were comparable with respect to age, height, weight, sex and ASA physical status. The incidences of pain on pretreatment drug injection was higher in the fentanyl group (33.3%) compared with lignocaine and normal saline ($P < 0.05$). The lowest incidence of pain on propofol injection was observed in the lignocaine pretreatment group (14.3%) compared with fentanyl (42.9%) and normal saline (71.4%) ($P < 0.05$). There was no significant difference in adverse skin reaction within groups. In the normal saline pretreatment group, 38.1% of the participants experienced severe pain, compared with 9.5% in the fentanyl ($P < 0.05$) group; none with lignocaine. The number needed to treat was 2 in the lignocaine pretreatment group compared with 4 in the fentanyl pretreatment group.

Conclusion: Compared with fentanyl, lignocaine pretreatment was more effective in preventing pain on propofol injection.

Key words: Fentanyl, lignocaine, propofol

INTRODUCTION

Propofol is currently one of the most common intravenous anesthesia induction agents used, preferred for its smooth onset of action and rapid clear-headed recovery. But, pain on its injection is a common problem in adults, which varies between 30 and 90%.^[1]

Several strategies have been suggested to prevent or reduce pain at the site of propofol administration. Most previous and recent work in this area has been performed on the adjuvant use of hypnotic, analgesic, anti-inflammatory or local anesthetic drugs, which include adding lignocaine to propofol, cooling or warming propofol, diluting the propofol solution, injection of propofol into a large vein and pretreatment with intravenous injection of lignocaine, ondansetron, metoclopramide, opioids, magnesium or thiopentone with or without tourniquet; granisetron, metoclopramide, magnesium, ketorolac, dexamethasone or thiopentone – all have been tried with variable, and sometimes conflicting, results. Several studies have demonstrated the presence of opioid receptors in the primary afferent nerve endings in peripheral tissues.^[2-14]

Fentanyl is a short-acting pure opioid agonist commonly used for intraoperative and postoperative systemic analgesia. Also, it has some peripherally mediated analgesic action within the clinical dosage range.^[15] Lignocaine is a short-acting local anesthetic agent; when injected into a vein prior to propofol administration, it can reduce pain due to its local anesthetic action.^[1,2,16]

Pain on injection of propofol can be immediate or delayed. Immediate pain probably results from a direct irritant effect whereas delayed pain probably results from an indirect effect via the kinin cascade. Delayed pain has a latency of between 10 and 20s. Despite this discomfort, the incidence of venous sequelae, such as phlebitis, is <1%.^[17,18]

The present study objectives was to study the effect of pretreatment with preservative-free lignocaine 2%, fentanyl and normal saline as placebo, using the venous retention technique for prevention of pain on propofol injection.

MATERIALS AND METHODS

This study was conducted at the Department of


Anaesthesiology of a tertiary care postgraduate teaching Hospital, Kolkata, between January 2008 and September 2008. The number of participants required in each group was determined using PS – “Power and Sample Size Calculation” – software (Version 2.1.30, February 2003). The sample size required for correctly rejecting the null hypothesis (of equal incidences of pain on propofol injection) with the probability of 90% (i.e., power of 90%) was calculated based on the following assumptions. The incidence of pain on propofol injection in a previous study by Fletcher *et al.* (1984) was 85%.^[19] Another study by Pang *et al.* (1998) found that the incidence of pain on propofol injection on pretreatment with fentanyl was 34%.^[1] With $\alpha=0.05$, i.e. probability of Type 1 error=5%, and the ratio of control to experimental participants equal to one in each group, it was determined that 21 participants in each group were required. Inclusion Criteria: Participants of the age group of 18–60 years of either sex, ASA physical status 1 and 2 undergoing elective surgery under general anesthesia. The Exclusion Criteria: The following participants were excluded from the study:

- i) Unwilling participants.
- ii) Participants with severe respiratory, cardiovascular, neurological or renal disease (ASA physical status 3 and 4).
- iii) Participants with a history of allergy to any of the study drugs.
- iv) Hemodynamically unstable participants.
- v) Participants having analgesia before surgery.
- vi) Participants with difficult and/or more than one trial of venous cannulation with 18G IV cannula satisfactorily in any large peripheral vein of the hand.
- vii) Pregnant women.

This study is a randomized, prospective, double-blind, placebo-controlled, parallel-group study ($n=21$ in each group). The primary outcome variables are:

- i) Incidence of pain on pretreatment drug injection in each group.
- ii) Four-point pain score in the placebo control (saline), fentanyl, in lignocaine groups to assess severity of pain on propofol injection as follows: 1 – No pain, no reaction to injection. 2 – Slight pain (minor verbal or facial response). 3 – Moderate pain (clear verbal or facial response). 4 – Severe pain (patient complains of pain and withdraws the arm).

Visual analogue scale (VAS) was not used as it appears to be sensitive to smaller changes in effect over time than are categorical measures. A four-point categorical scoring system was chosen in this study rather than the VAS system as it was very simple to use. Appropriate hand–eye coordination required for recording the VAS score might not be present in all participants during the rapidly changing state of consciousness during anesthesia induction.^[19,20]

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After approval of the institute's ethical committee and obtaining written informed consent, 21 participants in each of the three groups were enrolled for the study. Participants underwent thorough preoperative evaluation and were checked against the exclusion criteria of this study. In the operating room, after cleansing of the local area with 70% alcohol, venous cannulation was done in a large peripheral vein of the hand using an 18G polyurethane intravenous cannula, and intravenous drip with Ringer Lactate was started at 100 mL/h. To ensure blinding, coded syringes containing test drugs were prepared by an anesthesiologist not involved in evaluation of the pain score. Participants of group A received 2 mL of 2% lignocaine (preservative free) intravenously. Participants of group B received 2 mL fentanyl (100 mcg) intravenously. Participants of group C received 2 mL normal saline intravenously. Participants were randomized into three groups to receive, intravenously, either lignocaine (40 mg) or fentanyl (100 µg) or placebo (normal saline). The randomization list was generated by a random number function using the Microsoft Excel 2003 spreadsheet, resulting in a list of 63 assigned to participants receiving the drugs. Identical-looking coded syringes were prepared by an anesthesiologist not involved in the study. Venous occlusion of the arm proximal to the puncture site was maintained with a blood pressure cuff inflated to 40 mmHg as veins over the dorsum of the hand were used for the pretreatment drug injection. The study drugs or placebo were injected over 30 s and venous occlusion was released after 1 min of completion of the pretreatment drug injection. The patient was assessed for any pain to the pretreatment drug. After 1 min, the venous occlusion was released and propofol (2 mg/kg) at room temperature was administered through the intravenous cannula. During a 10-s pause after the first 25% of the calculated propofol dose, the patient was assessed according to the four-point pain score. In the present study, long chain triglyceride (LCT)-based propofol formulation was used in all participants. Thereafter, induction of anesthesia was continued with the remainder of the calculated dose of propofol. Atracurium 0.5 mg/kg intravenous injection was used for muscle relaxation to facilitate tracheal intubation. Anesthesia was maintained with halothane 0.5% and 66% nitrous oxide with oxygen on controlled ventilation with intermittent bolus of atracurium. Intraoperative analgesia was maintained with incremental doses of fentanyl 50 µg as intravenous injection. At the end of surgery, inhalational agents were discontinued and neuromuscular blockade was reversed with injection neostigmine 0.5 mg/kg plus injection glycopyrolate 0.01 mg/kg intravenously. The participants were extubated and transferred to the recovery area after confirmation of satisfactory recovery criteria. The injection site was checked for pain, edema, and wheal and flare response after one hour of induction by a person blinded to the group assignment.

Data Analysis expressed as follow: Demographic data were expressed as mean±SD (age, weight, height) or proportion (sex and ASA physical status). Incidences of severe pain and milder degrees of pain on injection of propofol (grades 1–4 on a four-point pain scale) were expressed as proportions (percentage) of the total number of participants in each study group. Parametric data were analyzed by ANOVA, followed by Bonferroni's and Tamhane's *post hoc* analysis. Categorical data were analyzed using the Chi-square test. Comparison was made using Phi and Cramer's V statistics after cross-tabulation for the incidences of pain and skin reaction on injection of pretreatment drugs and the pain associated with propofol injection in participants pretreated with either normal saline or fentanyl or lignocaine intravenously. The severity of pain on propofol injection was compared among the three groups using Kendall's tau b statistics. Processing of study data and statistical analysis was carried out using the "SPSS version 13.0 (2004) for Windows" statistical software and Quickcalcs online calculator for scientists from Graphpad software to calculate the number needed to treat (NNT).^[21]

RESULTS

There were 63 participants ($n=63$) divided into three equal groups of 21 participants ($n=21$) each. It was observed that there was no statistically significant difference between the groups with respect to age, height, weight, sex and ASA physical status analyzed by ANOVA followed by Bonferroni's and Tamhane's *post hoc* analysis [Table 1].

The incidences of pain on pretreatment drug injection were, group A (fentanyl)=33.3% (seven of 21), group B (lignocaine)=9.5% (two of 21) and group C (normal saline)=0% (none of 21). Applying the nominal by nominal Phi Cramer's V test for the incidences of pain of pretreatment drug injection in the three groups, the differences between the groups (group A vs. group B, group B vs. group C and group C vs. group A) were statistically significant ($P<0.05$) [Table 2].

The incidences of pain on propofol injection were, group A=42.9% (nine of 21), group B=14.3% (three of 21) and group C=71.4% (15 of 21) [Table 3]. The lowest incidence of pain on propofol injection was observed in group B (lignocaine pretreatment group), whereas group C (normal saline pretreatment group) experienced the highest incidence of pain on propofol injection. Applying the nominal by nominal Phi Cramer's V test for the incidences of pain on propofol injection in the three groups, the differences between the groups (group A vs. group B, group B vs. group C and group C vs. group A) were statistically significant ($P<0.05$) [Table 3].

The incidences of skin reaction within 1 h of the pretreatment drug injection were, group A=14.3%

(three of 21), group B=4.8% (one of 21) and group C=0% (none of 21). The differences in the incidence of skin reaction in the three groups analyzed by the nominal by nominal Phi Cramer's V test were not statistically significant ($P=0.154$) [Table 4].

Analysis of the incidences of severe pain (score 4) on the propofol injection revealed that in group C (normal saline pretreatment group), 38.1% (eight of 21) participants experienced severe pain, 9.5% (two of 21) of the group A participants (fentanyl pretreatment group) experienced severe pain and none of the group B participants (lignocaine pretreatment group) experienced severe pain. The differences between the three groups (group A vs. group B, group B vs. group C and group C vs. group A) analyzed using the ordinal by ordinal Kendall's tau b test were statistically significant ($P<0.05$). The incidence of moderate pain (score 3) in group A was 14.3% (3 of 21), group B was 0% (none of 21) and group C was 23.8% (five of 21). The differences between the three groups (group A vs. group B, group B vs. group C and group C vs. group A) with regards to the incidence of moderate pain analyzed by the ordinal by ordinal Kendall's tau b test were statistically significant ($P<0.05$). The incidence of mild pain (score 2) in group A was 19.0% (four of 21), group B was 14.3% (three of 21) and group C was 14.3% (three of 21). There were no statistically significant differences between the three groups (group A vs. group B, group B vs. group C and group C vs. group A) with regards to the incidence of mild pain analyzed by the ordinal by ordinal Kendall's tau b test ($P>0.05$) [Table 5].

Comparison of NNT on the severity of pain on propofol injection following pretreatment with fentanyl and lignocaine compared with normal saline was performed.

In the fentanyl (group A) group, 71.43% of the control subjects had adverse outcomes, 42.86% of the experimental subjects had adverse outcomes and the absolute risk reduction was 28.57% (95% confidence interval (CI) – 0.09–57.23%). The NNT was 4, which means that about one in every four participants will benefit from the treatment.

In the lignocaine (group B) group, 71.43% of the control subjects had adverse outcomes, 14.29% of the experimental subjects had adverse outcomes and the absolute risk reduction was 57.14% (95% CI – 32.70–81.58%). The NNT was 2. This means that about one in every two participants will benefit from the treatment [Table 6].

DISCUSSION

Our study demonstrates the incidences of pain on pretreatment drug injection were higher in the fentanyl group (33.3%) compared with the lignocaine and normal saline ($P<0.05$) groups. The lowest incidence of pain

Table 1: Demographic characteristics and comparison of participants

Demographic parameter	Group mean \pm SD or proportion	Statistical test
Age (years)	Group A=40.6 \pm 11.4 Group B=42.2 \pm 9.5 Group C=43.1 \pm 10.0	ANOVA: $P=0.73$ Post hoc: $P>0.05$
Height (inches)	Group A=62.9 \pm 2.7 Group B=61.5 \pm 2.7 Group C=62.4 \pm 2.6	ANOVA: $P=0.24$ Post hoc: $P>0.05$
Weight (kg)	Group A=56.8 \pm 4.6 Group B=55.0 \pm 5.6 Group C=57.9 \pm 6.7	ANOVA: $P=0.25$ Post hoc: $P>0.05$
Sex (M:F)	Group A=14:7 Group B=9:12 Group C=9:12	Pearson Chi-square: $P=0.20$ Phi Cramer's V test: $P=0.20$
ASA physical status (ASA 1:ASA 2)	Group A=18:3 Group B=16:5 Group C=14:7	Pearson Chi-square: $P=0.20$ Phi Cramer's V test: $P=0.20$

Group A = fentanyl pretreatment; Group B = lignocaine pretreatment; Group C = normal saline pretreatment

Table 2: Comparative incidences of pain of pretreatment drug injection

Pretreatment drug	No pain on pretreatment drug injection (%)	Pain on pretreatment drug injection (%)
Fentanyl (group A)	14 (66.7)	7 (33.3)
Lignocaine (group B)	19 (90.5)	2 (9.5)
Normal saline (group C)	21 (100)	0 (0)

Table 3: Comparative incidences of pain on propofol injection following pretreatment with fentanyl, lignocaine or normal saline

Pretreatment drug	No pain on propofol injection (%)	Pain on propofol injection (%)
Fentanyl (group A)	12 (57.1)	9 (42.9)
Lignocaine (group B)	18 (85.7)	3 (14.3)
Normal saline (group C)	6 (28.6)	15 (71.4)

Table 4: Comparative incidences of skin reaction within 1 h of the pretreatment drug injection

Pretreatment drug	No skin reaction (%)	Skin reaction (%)
Fentanyl (group A)	18 (85.7)	3 (14.3)
Lignocaine (group B)	20 (95.2)	1 (4.8)
Normal saline (group C)	21 (100)	0 (0)

on propofol injection was observed in the lignocaine pretreatment group (14.3%) compared with the fentanyl

Table 5: Comparison of the severity of pain on propofol injection following pretreatment with fentanyl, lignocaine or normal saline

Pretreatment drug	Number of participants within each group: Four-point pain score (%)			
	1 (no pain)	2 (mild pain)	3 (moderate pain)	4 (severe pain)
Fentanyl (group A)	12 (57.1)	4 (19.0)	3 (14.3)	2 (9.5)
Lignocaine (group B)	18 (85.7)	3 (14.3)	0 (0)	0 (0)
Normal saline (group C)	5 (23.8)	3 (14.3)	5 (23.8)	8 (38.1)

Table 6: Comparison of the number needed to treat on the severity of pain on propofol injection following pretreatment with fentanyl, lignocaine compared with normal saline

Parameters	Fentanyl (group A)	Lignocaine (group B)
Adverse outcome in the experimental group	42.86%	14.29%
Adverse outcome in the control group	71.43%	71.43%
Absolute risk reduction (95% confidence interval)	28.57% (-0.09%–57.23%)	57.14% (32.70–81.58%)
Number needed to treat	4	2

(42.9%) and normal saline (71.4%) ($P < 0.05$) groups. In the control group, 38.1% of the participants experienced severe pain compared with 9.5% in the fentanyl ($P < 0.05$) group, and there were no such incidences with lignocaine. These observations corroborated with the previous studies where the incidence of pain on intravenous injection of fentanyl, lignocaine and normal saline was 34%, 11% and 0%, respectively. The lowest incidence of pain on propofol injection was observed in group B (lignocaine pretreatment group, 14.3%), whereas group C (normal saline pretreatment group, 71.4%) experienced the highest incidence of pain on propofol injection. Participants in group A (fentanyl pretreatment group) had a lower incidence of pain (42.9%) than group C (normal saline pretreatment group, 71.4%), but still higher than that in group B (lignocaine pretreatment group). Both lignocaine and fentanyl pretreatment reduced pain on propofol injection, with lignocaine pretreatment being more efficacious.^[1,2] Others reported that intravenous lignocaine was the most commonly used pretreatment, but had a failure rate of 13–32%.^[11]

The effectiveness of lignocaine and fentanyl are consistent with the reports of others who also reported that lignocaine and fentanyl were effective in reducing the intensity of propofol injection pain.^[1,2,22,23] But, few other studies concluded that fentanyl pretreatment was not found to be effective in reducing pain on propofol injection.^[24,25] It may be noted that in one of the former studies, venous retention technique for the pretreatment drugs was not used, which might account for the difference in the result.^[24]

In the present study, 38.1% of the participants had severe

pain (score 4) and 23.8% had moderate pain (score 3) on propofol injection in the normal saline group compared with 9.5% participants with severe pain and 14.3% with moderate pain in the fentanyl group. None of the participants in the lignocaine group experienced severe or moderate pain, proving more efficacious than fentanyl in this respect. These findings were similar to that in the studies by researchers in the same field.^[1,20,22]

The incidence of mild pain was similar in the three study groups. Skin erythema and/or wheal were observed in three participants in group A, one participant in group B and none in group C participants. This was similar to the study findings of Pang *et al.*^[1]

We also calculated the NNT in our study. For convincing results of our study, the NNT was 2 in the lignocaine pretreatment group compared with 4 in the fentanyl pretreatment group. Coverage of this expression of the number of participants who must be treated to prevent one adverse event provides prospective readers with added information to facilitate them in making a decision as to whether a management protocol can be used in another set up, otherwise may influence the interpretation of the study results.^[26-29]

We had several limitations. Many factors can affect the incidence of pain, which include site of injection, size of vein, speed of injection, buffering effect of blood, temperature of propofol and concomitant use of drugs such as local anesthetics and opioids, all of which could not be get rid of.

Different methods have been used to decrease the discomfort of pain for drug-pretreatment by brief venous retention with tourniquet, which is used prior to propofol injection, that isolates the forearm veins from the rest of the circulation. It presents a useful model for studying the peripheral actions of a drug in the absence of a central effect. Briefly applied venous tourniquet does not cause pain by itself. Although this technique is straight-forward in elective surgery and adult participants, its clinical applicability in emergency induction and children remains doubtful. Further studies are needed to establish the feasibility of this technique in children and emergency induction of anesthesia.

In conclusion, lignocaine 40 mg or fentanyl 100 mcg retained in the tourniquet-occluded veins for 1 min effectively reduce pain on propofol injection compared

with the normal saline placebo. Compared with fentanyl, lignocaine is more effective in preventing pain on propofol injection. Compared with fentanyl, lignocaine pretreatment was more effective in preventing pain on propofol injection.

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